Physiologie moléculaire de la réponse immune et des lymphoprolifération

Rapport Hcéres

agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit

Physiologie Moléculaire de la Réponse Immune et des lymphoprolifération

From the

University of Limoges

CNRS

February 2011

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From the

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

February 2011

Research Unit

Name of the research unit: Physiologie Moléculaire de la Réponse Immune et des lymphoprolifératıons

Requested label: UMR CNRS

N° in the case of renewal

Name of the director: M. Michel COGNE

Members of the review committee

Committee chairman

M. Joost van MEERWIJK, University Toulouse 3, France

Other committee members

M. Thierry DEFRANCE, Université de Lyon 1, France

M. Thierry NAAS, CHU Bicêtre, Le Kremlin Bicêtre, France

M. Ulrich BLANK, Université Paris 7, Paris, France, CoNRS representative

M. Yvon LE BRANCHU Université de Tours, France

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M. Ahmid SIAHMED, CHU

Ms. Marie SENGELEN, CHU

Le membre du CNU n'a pas pu se déplacer

Report

1 • Introduction

- **Date and execution of the visit:**

The visit started on February 15, 2011 at 8:30 am and ended on the same day at 2 :15 pm. The scientific program included an overall presentation of the Unit by its Director followed by two scientific presentations of the past activity and projects by each one of the two team leaders. Three parallel meetings with PhD students and postdocs, with engineers, technicians and administrative staff, and with researchers with permanent positions were also organized. At the end of the site visit next day, representatives of the supporting bodies (CNRS, University, and University Hospital) met with the committee.

- **History and geographical localization of the research unit, and brief presentation of its field and scientific activities**

This research unit is located in a single building within the Limoges Health and Life Science campus that also includes the University Hospital. It brings together two teams headed by 2 MD/PhDs. The research topics are focused on normal and pathophysiological aspects of B cell differentiation with a strong emphasis on the physiology of Ig genes loci. The Unit addresses both basic questions relating to Ig gene regulation and more applied issues concerning hematological diseases such as B cell lymphomagenesis and Ig deposition diseases. It has also developed a very strong expertise in creation of transgenic mouse models. This research unit is a member of the GEIST super-structure (SFR) that includes all university teams working in the field of Biology and Health. It also participates to the Cancéropôle Grand Sud-Ouest. Surfaces given to the unit have significantly increased with years, from 400 to about 800 square-meters, but on two different floors, and with relatively low standards. Of note, the animal facility was destroyed 1 year ago resulting in 95% of animals and work loss. All PhD students belong to the Biology and Health Doctoral School linked to the PRES Limoges-Poitiers.

- **Management team**

The head of the Unit is M. Michel COGNE. The unit does not have a lab council but all unit members gather several times a year to discuss scientific strategy. A scientific advisory board was appointed last year. An ad hoc scientific board assessed the Unit last year.

- **Staff members**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	9	11
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	8	8
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	6
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	6	
N6: Number of Ph.D. students (Form 2.8 of the application file)	11	
N7: Number of staff members with a HDR or a similar grade	7	11

2 • Overall appreciation on the research unit

- **Summary**

Location of the laboratory within the Limoges Health and life Sciences campus that also includes the University Hospital facilitates both the interactions between clinicians and researchers and the collection of human specimens. This Unit brings together two teams led by MD/PhDs involving around 50 people altogether who work on different aspects of B cell physiology and physiopathology. Team 1 is focused on basic research with a primary interest in the physiology of the Ig heavy chain locus but also related diseases, in particular Ig deposition diseases. It has generated a variety of original transgenic animal models. Team 2 is orientated towards clinical studies on lymphomagenesis but also conducts basic research focused on the cellular targets of EBV. The scientific output is very good to excellent especially regarding the relatively small size of the Unit : numerous high quality publications, 3 patents issued, creation of 1 start-up.

Publications are mostly in good specialty journals but also include one paper signed in leading position in the high profile New England Journal of Medicine (IF 47) as well as two collaborative publications in the very high impact journals Nature and Immunity. Within its field of research, the Unit is very competitive and has a good international visibility illustrated by the papers signed in collaboration with high-profile researchers. Very good contacts with the clinical partners and a very strong implication of clinicians in the research pursued by the Unit. The projects are scientifically relevant with a very good interface between basic science and patient-orientated research. However, the committee noticed a tendency to undertake a large number of projects and to potentially underestimate the scale of the task, which may endanger the competitiveness of the group.

- **Strengths and opportunities**

- The very strong expertise of Team 1 in generating transgenic mice with insertions or deletions at the Ig VH locus has led to the establishment of unique transgenic models. The strong implications of the Unit in developing mouse models of hematological diseases.

- The good balance between clinical and more fundamental research.

- The very good scientific output of the Unit and its strong collaborative links with high-profile foreign and national research teams.

- The good translational activity both with industry (e.g. creation of a start-up) and with the clinics.

- Both team leaders substantially contribute to the structuration of biomedical research at the local level.

- Opportunity: the research unit will move to a new building in a few years.

- **Weaknesses and threats**

- Although unique, some of the transgenic models (for example, IgE humanized transgenics) are incomplete and need further development (i.e.crossing with humanized Fc-receptor transgenic mice) for further understanding of the physiology.

- The EBV projects of team 2 should be more focused as they are likely to face heavy international competition.

- A tendency to undertake too many projects.

- The accidental fire has jeopardized some of the ongoing research projects.

- **Recommendations**

- Given the human resources of the Unit, the committee recommends that it keeps focusing on a relatively limited number of projects.

- Although there is a strong expertise in the elaboration of transgenic mouse models relating to the Ig genes locus, the connection of studied regulatory elements with external signals (BCR, cytokine-R etc...) is only partially exploited and could be worthwhile to develop in the future.

- Partnership in the analysis of humanized Ig models (i.e. humanized FcεR1 models as human IgE does not bind to the mouse FcεR1) may be necessary.

- Given the understandable difficulty to attract foreign speakers for international seminars (due to geographical location), organization of journal clubs in English language should be envisaged for training of young researchers. This may also foster post-doctoral studies abroad.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	10
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	3
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0.93
A4: Number of HDR granted during the past 4 years (Form 2.10)	4
A5: Number of PhD granted during the past 4 years (Form 2.9 of the application file)	14

3 • Specific comments

- **Appreciation on the results**

The publication rate is very good to excellent: 145 publications in the last 5 years, ¾ correspond to clinical studies and ¼ to basic science. The quality of the publications is high: members of the Unit have authored (New England Journal of Medicine) or co-authored (Nature, Immunity) 3 papers in outstanding generalist and specialist journals with a very high impact factor. They also hold principal authorship in very good specialist (Blood, Leukemia, Haematologica, Cell Death and Differentiation) and generalist journals (PNAS). Besides these "primary" publications, the Unit's members have contributed to a substantial number of reviews in French, mostly medical journals, to many oral and poster-communications in national and international congresses, some of which as invited speakers. Combined, these communications illustrate well the (inter)national visibility of this Unit.

Both teams have a very good training output : 13 PHD thesis have been defended in the Unit in the last 5 years. 12 of them were associated with publications or patents. Excellent translational activity illustrated by: 3 patents issued and the creation of one start-up biotech company.

This Unit's contribution to our understanding of the control of the mouse Igh-locus appears very original. Its unique expertise in mutational analysis of this locus, besides the possibility to engage competitive fundamental projects also gives the Unit the opportunity to study pathologies such as Ig deposition diseases, which may have significant impact. The work on molecular aspects of EBV-induced lymphomas is interesting but the immediate relevance of the studies on the characterization of B-cell lymphomas is less clear to the committee.

The Unit has proven its ability to establish and maintain stable partnerships with high profile collaborators both nationally (Teams 1 and 2) and internationally (Team 2).

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

The unit recently recruited an assistant professor (MCU) position with a chair of excellence of the CNRS. Two of the Unit's members obtained a research bonus (PEDR), reserved for University personnel with a real and productive scientific activity. Together with the eleven invitations to French conferences, these observations attest of a very good national visibility and recognition of the Unit and its members. Members of the Unit have also been invited to international congresses (n=9), confirming the international recognition.

The Unit comprises 12 PhDs and 5 post-docs but its ability to recruit high levels scientists from abroad is moderate. Most of these researchers are locals and it appears therefore that despite the excellent scientific qualities of the Unit, it remains difficult to attract scientists from elsewhere. However, despite its localization in the French center region, the Unit has managed to recruit 12 PhD-students and 5 post-docs. This confirms that the local/national attractiveness of the Unit is very good.

The links with international partners is very good as well. The Unit has established a very strong expertise and international reputation in the generation of transgenic mice with insertions or deletions at the Ig VH locus. This gave them the opportunity to create a very large number of national and international links during the evaluation period. The Unit has been reinforced by team 2 for the axis on lymphomagenesis and the study of the mechanisms of EBV-mediated transformation. The scientific quality of the work produced since 2006 is very good to excellent. Some outstanding publications result from their participation in collaborative work established on the basis of their competence in transgenic mouse models (Nature, Immunity).

The unit has proven its excellent capacity to attract robust extramural fundings (800 000 euros approximately in the past 2 years), i. e. more than 4 times the budget alloted by the Institutional partner of the Unit (CNRS). They were obtained from the following sources: National funding agencies, INCA and ANR (38%), local funding agencies (33%) charities (16%), The European Community (7%).

The unit has developped strong links with local, national and international partners :

- Long-lasting collaborations with three well-recognized teams in Germany and in the USA;

- Federation by of different clinicians and researchers nationwide on the topic of MZ B cell lymphomas;

- Scientifically relevant transversal collaborations with several members of the GEIST IFR;

- Collaborations with 3 well-recognized French teams in Strasbourg (DNA repair), in Paris (epigenetics) and in Marseille-Luminy (high throughput genomics and VDJ recombination) to develop novel techniques of functional exploration of the genome (3D-FISH, 3C, Chip-on-chip). These examples attest of an excellent networking capacity of the Unit.

Concrete results of the research activity and socio-economic partnerships include :

- Research Tools: Transgenic mouse models to explore: i) the impact of regulatory regions on Ig isotype switching, somatic hypermutation and deregulation of oncogenes, ii) the differentiation programs linked to the IgA and IgE BCRs; Transgenic mouse models for Ig deposition diseases;

- Clinical research: Cohorts of patients; B-cell lymphoma and amyloidosis specimen collections;

- Industrial applications: Humanized antibodies and related molecules; Development of cytometry applications for clinical studies; Three licensed patents; The set-up of a new biotech company “B cell design".

- **Appreciation on the management and life of the research unit**

The two teams work on strongly related but clearly distinct themes, justifying the organization. During the meeting with the members of the unit, it became clear that they appreciate the strong links and the good balance between clinical and more fundamental research. They also appeared generally satisfied with the management. Combined with the excellent scientific production and the strong implication in the local research area (IFR/SFR), the committee therefore concludes that the management is appreciated and efficient.

Lab meetings are regularly organized to discuss scientific issues. However, journal clubs are not organized on a regular basis. This issue may need improvement.

Excellent teaching activity of the Unit’s members: 10 out of the 17 researchers with a permanent position have teaching duties at the University or at the Medical School. Very strong implication as well in structuration of research at the local level: the head of the unit was the head of the IFR 145 (GEIST) between 2007 and 2010 and another unit member is now taking over this position. The head of the unit has also assumed the function of Vice-President of the Limoges University in charge of the Scientific council. Lab meetings are regularly organized to discuss scientific issues. However, journal clubs are not organized on a regular basis.

- **Appreciation on the scientific strategy and the project**

The proposed scientific projects are mostly based on the existing ones but give new original impetus to them. For example, team 1 will investigate the mechanisms by which non-functional Igk transcripts inhibit plasma cell development, will develop novel animal models for lymphoma and immunoglobulin deposition diseases, and will develop mutant mice to study the role of distinct Ig isotypes. Team 2 proposes to investigate if different marginal zone lymphomas represent distinct entities and how they develop, as well as the molecular mechanisms of EBV-induced lymphomagenesis. Therefore, no major modifications are proposed but the project should allow the unit to maintain its excellent scientific production.

The expertise of the unit in genetic manipulation of the IgH locus allows for the development of several cutting edge projects, as discussed elsewhere. Its close links with the clinic favors development of several novel mouse models for B-lymphocyte dependent pathologies.

4 • Appreciation team by team

- **Title of the team and name of the team leader**
- **Genetics and physiology of B cells and lymphoproliferative disorders : M. Michel COGNE.**
- **Staff members**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	6	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	12	13
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	
N6: Number of Ph.D. students (Form 2.8 of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	5	9

- **Appreciation on the results**

The projects undertaken by the team in the past 4 years have focused on the functional role played by the cis-regulatory elements located within the immunoglobulin heavy chain locus during normal B cell development and differentiation as well as during lymphomagenesis. This work is cutting-edge science. The major achievements of the team are:

1. The demonstration of the crucial role played by the 3'regulatory region on B cell transformation that results from translocations of oncogenes onto the IgVH locus (Nature 2009, J. Immunol. 2007*).

2. The development of an animal lymphoma model in which the the IgH locus 3'regulatory region drives the c-myc transgene (J. Immunol. 2007*, Leukemia Resarch 2009*). The unit members showed that these mice developed Burkitt's-like lymphomas (2/3) and anaplastic plasmacytomas (1/3), but not on all genetic backgrounds.

3. The description of some of the long range interactions that occur between distinct cis regulatory elements of the Ig VH locus during class switch recombination (Immunity 2007, J. Immunol. 2009*, J. Immunol. 2010*, Blood 2010*).

4. The combined mRNA surveillance pathways for aberrant Ig transcripts (J. Immunol. 2010*).

5. The function of the IgA-class B cell receptor (BCR) in promoting plasma cell differentiation (PNAS, 2010*).

6. The development of a mouse model for Fanconi syndrome (Blood 2006, Contrib. Nephrol, 2011*)

(* Papers that unit members have signed as first and/or last author)

The team has also produced a very well recognized clinical research contribution in the field of therapy of AL amyloidosis (NEJM in 2007). Altogether, the team has demonstrated an amazing capacity to generate an impressive collection of transgenic mice harboring insertions or deletions in the Ig VH locus to address fundamental questions of B cell biology. The originality of the research conducted by this team is beyond any doubt, it is one of the leading groups along with P. Ferrier at CIML, F. Alt or M. Nussenzweig in the USA in the field of physiology of the Ig locus. The

impact on the scientific community is high as illustrated by the paper they have published in collaboration with Fred Alt in Nature.

Excellent publication record: 93 papers published in the past 4 years with members of the team appearing as leading authors in 40 % of them. 22 papers with the name of the PI on them. Two papers published in collaboration in top journals : Immunity and Nature. 11 papers published as leading authors in very good specialty journals: Blood (2), PNAS (2), J. Immunol (5), Haematologica (1) and in the very high IF medical journal New England Journal of Medicine.

The long-term collaboration with the laboratory of F. Alt remains very fruitful. Also several other high quality collaborations yield excellent publications, as cited before. Therefore, despite the geographically rather isolated situation (as also acknowledged by the staff-scientists), scientifically this team appears to be among the leading teams in the analysis of the IgH locus.

- **Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners**

The PI enjoys a good international visibility: 3 invited seminars given at international conferences and 3 at national symposia, a long-lasting collaboration with the high-profile lab at the Howard Hughes in Boston. Multiple oral communications in clinical research meetings. The team's members have also been invited to write several reviews

Very good attractivity and very dynamic recruitment of young scientists especially given that the Unit is located in Limoges, i. e. quite remote from the identified/recognized immunological research centers. The team actually comprises 3 INSERM or CNRS researchers with permanent positions (CR1), 2 researchers with teaching duties (MC), 3 post-docs, 8 PhD students. Unfortunately, the attractivity of the Unit for scientists from outside Limoges remains quite limited, which is probably explained by its localization.

Substantial funding has been obtained from several foundations, the ANR, the INCa, the European Union, and other sources. The team has obtained contracts from CAYLA-INVITROGEN, has an ongoing collaboration with Dendritics, is part of the industrial cluster Cancer Bio-Santé, and has a contract with the ANRS.

The team has a long-standing collaboration with a laboratory at Harvard University, participates to the EURAMY STREP network, hosts a National Reference Center on amyloidosis, and coordinates a PHRC. Therefore, active networking is clearly an important activity.

Team 1 has 2 patents that have been licensed to industrial partners. The quality of the socio-economic partnerships is best illustrated by the spin-off of the team (« B cell design »). Therefore, the committee feels that this team has an excellent research activity.

- **Appreciation on the scientific strategy and the project**

During the next 5 years, the members of this team will focus on several complementary projects that are described below :

Regulation of Ig locus expression and remodeling: concerns the analysis of the long-distance influence of mutations introduced in the IgH locus (3'RR, Eμ, MAR) as well as collaborative studies to analyze locus accessibility (Chromosome conformation capture (3C) analysis, 3D-FISH, ChIP-Sequencing. The influence of these elements on long range interactions regulating locus remodeling, transcription, recombination or somatic hypermutation will be studied. Another transgenic model transferring switch-competent elements into switch-incompetent loci will explore the minimal elements necessary for class-switching.

B cell Lymphoma models: During the next 5 years, the members of the unit will (1) study the role of BCR antigen-mediated signals, (2) study the role of BCR « tonic » signals, (3) try to identify potential 3'RR modulators using siRNA library screening, and (4) study the occurrence and oncogenicity of translocations in 3'RR-deficient animals (pristane-induced plasmacytomas in 3'RR mice after backcrossing on the BALB/c background).

Abnormal Ig deposits in tissues: multivisceral tissue deposit, tubulopathies, and crystal-storing histiocytosis (Ig crystals within phagocytes). During the past period, the members of the team have successfully generated a mouse model of Fanconi syndrome (Blood 2006*). However, attempts to generate a mouse model for AL amyloidosis have been

unsuccessful so far. During the next 5 years, more efforts will be dedicated to the latter project. The team members will also attempt (1) to generate new models for LCDD and Cast nephropathy, (2) to develop a new therapy for amyloidosis, and (3) to further elucidate the mechanisms of IgA nephropathy.

Functional specificities of the IgA and IgE BCR: The team has generated knock-in mice in which human IgA or IgE substituted membrane IgM to study the impact of these Ig isotypes on B cell development and mature B cell fate. They will also generate mice expressing a chimeric BCR in which the cytoplasmic tail will either be that of IgM or IgA. They will follow the fate of B cells in these animals.

The project of the team logically follows the work undertaken in the past four years. It is very ambitious but its feasibility is good owing to the expertise, tools and murine models the group has generated over the years. Nevertheless, care should be taken not to underestimate the task of defining the minimal regulatory elements required for CSR inasmuch as it relies on creation of a novel transgenic strain of mice for each novel construction to be tested. The project on mRNA surveillance, although of great fundamental interest, is somehow disconnected from the core topic of the team.

- **Conclusion:**

  - Summary

The committee feels this is an excellent team.

  - Strengths and opportunities

The capacity to feed its basic research with interrogations raised from the clinics (the development of mouse models reproducing certain Ig deposition diseases for instance).

Outstanding expertise in the generation of transgenic mouse models.

The vitality of the team.

  - Weaknesses and threats

The relatively high number of projects (6 subprojects) and the possible scientific dispersion that may result from it.

Obviously the destruction of the animal house by a fire and the loss of some of the transgenic cell lines is a major drawback and has slowed down some of the projects.

  - Recommendations

Continue to build on original research questions in connection with the available animal models, the main expertise and originality of the unit. This may eventually also require to analyze the pathways by which BCR/Cytokine signaling impacts on regulatory and switch elements during B cell development. Continue to keep strong interactions between basic research and clinics.

- **Title of the team and name of the team leader**
- **Molecular mechanisms of lymphomagenesis : M. Jean FEUILLARD.**
- **Staff members**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	6	7
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	3
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.8 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

Team 2 works on B cell lymphomagenesis and more specifically (1) on EBV and B-cell transformation and (2) on marginal zone B-cell lymphomas.

EBV and B-cell transformation: Previous studies have shown that LMP1 signaling is critical in B-cell lymphomagenesis. In this respect, team members have tried (1) to identify transcriptional factors targeted by LMP1, (2) to identify target genes, (3) to elucidate the effects of LPM1, (4) to determine the differences between LMP1 variants, and (5) to elucidate the interactions between NF-¤B and LMP1. During the past 5 years, team members have shown that (1) LMP1 induces NF-¤B resulting in the induction of STAT1 and p53, (2) STAT1 and p53 cooperate to induce apoptosis, (3) NF-¤B, STAT-1 and p53 increase CD95 expression and CD95 sensitizes EBV-immortalized B cells and T cell killing and (5) induction of CD95 overexpression by LMP1 induces CD95 autoactivation and apoptosis. Altogether, these results suggested that LMP1 is an ambivalent oncogene and that NF-¤B and c-myc are two master transcriptional factors of EBV latency III immortalized B-cells.

Marginal zone B-cell lymphomas: Previous studies have suggested that different entities of indolent B-cell lymphomas are derived from memory B cells. Pathogenesis of Splenic Marginal Zone Lymphomas (SMZL), Nodal Marginal Zone Lymphomas (NMZL), and Lympho Plasmacytic Lymphomas (LPL) remains incompletely characterized. During the past 5 years, the members of team 2 (1) have shown that plasma cell differentiation is a poor prognosis factor in Marginal Zone Lymphomas (MZL), (2) have described different aspects of SMZL, (3) have demonstrated that SMZL and LPL/WM originate from B-cell compartments with two different antigen-exposure histories, and (4) have contributed to the elucidation of the relationship between ZAP-70, IgVH somatic mutation status and cytogenesis in B-cell Chronic Lymphocytic Leukemia (CLL).

Main achievements of the team

- Immunophenotyping, mutational status and gene expression patterns of indolent B cell lymphomas (Leukemia 2008, Histopathology 2009).

- Optimized flow cytometry method for analysis of ZAP70 expression in CLL (Haematologica 2007).

- Demonstration that the EBV oncogene LMP1 upregulates NF¤B and sensitizes EBV-immortalized B cells to T cell killing via upregulation of Fas thus behaving as an ambivalent oncogene (Blood 2006, Cell Death Diff. 2007, J. Virol. 2008, Haematologica 2009, Cancer Research 2009).

- Demonstration that NF-kB and c-myc are two master transcriptional regulators of EBV latency III immortalized B-cells (J. Virol. 2009).

The team has developed expertise in the field of EBV-related B cell transformation and dissection of the cellular interactors as illustrated by the very good quality of the journals in which this work was published. It has also developed a relevant and fruitful collaboration with a well-recognized German specialist in the field (G. Bornkamm).

The overall output of the team's research is qualitatively and quantitatively very good. It has a good national presence but efforts must be made to achieve a better international visibility.

The overall scientific output of the team is good to very good. During the past 5 years, the team members have appeared in a total of 55 publications of which 24 papers in which the name of the PI appears. These 24 papers must be considered as the true production of this team, the others being mostly collaborative studies to which clinician members of the team have been associated. Members of the team sign as first or last authors in half of these 24 papers. All papers of the team are published in speciality journals but 1/3 of them are of good to very good quality (impact factor comprised between 8 and 10: Blood, Haematologica, Leukemia, Cell Death and Differentiation).

Team 2 has developed long lasting collaboration with industrial partners including Beckman Coulter and Amnis Corporation. One patent for a posteriori normalization of flow-cytometry data has emerged from this work.

- **Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners**

Members of the team have given 3 oral communications, of which one in an international meeting. The team's PI has given two invited seminars in international meetings. Combined, the team has a reasonable (inter)national visibility.

Team 2 has been able to recruit several students, 2 Maîtres de conférences (of which one with a Chair of Excellence) in 2005 and 2010, and 1 CNRS engineer in 2010. However, these people are mainly local and it remains difficult to attract scientists from outside of Limoges. Full time scientists remain absent.

Team members have obtained several grants during the past 5 years including funding from INCA, PHRC, STIC, ARC, INSERM/DOS, and contracts with industrial partners (Beckman Coulter, Amnis). The team leader is the PI of an INCA-funded PAIR lymphome project that brings together 10 french groups. Therefore, the finances of the team should not be a limiting factor in its activity.

Team 2 has developed several collaborations, mainly with French teams. It also collaborates with the Institute of Genetics and Molecular Biology of Tumors in Munich (Germany).

The work on development of flow-cytometry applications, in collaboration with industrial partners, has yielded four technical publications and one patent, the project on B lymphomagenesis, 8 publications in excellent specialty journals (Blood, J. Virol., Cell Death and Differentiation, Cancer Research), the project on marginal zone lymphomas, 3 publications in good specialty journals (Leukemia, Haematologica, The Hematology Journal, Histopathology). Given the size of the team, this technical and scientific production should be considered as very good.

- **Appreciation on the scientific strategy and the project**

Team 2 will develop two research axes. The first one deals with B-cell immune memory, BCR activation and indolent B-cell lymphomas. The second one deals with cellular activation, genetic alteration and B-cell lymphomagenesis. More specifically, the members of team 2 will attempt to answer the following questions: (1) Do SMZL, NMZL, LPL/WM constitute distinct entities? (2) What are the mechanisms involved in lymphomagenesis? (3) What are their normal counterparts? (4) Does antigen exposure play any role in their generation?

Clarity and focus of the project should be improved. The committee feels that the theme on marginal zone lymphoma gives too much weight to systematic investigations and data mining and should include more hypothesis-driven science. Owing to the high degree of competition in the field of EBV, definition of the project should be improved. Some concerns remain regarding the validity of the approach chosen to address the question of the immunogenicity of EBV-infected cells: focusing on a single molecule (B7H1) to explore the immunogenicity of EBV-infected B cells

appears of rather limited scope. The outcome of up-regulation of B7-1 on recognition of EBV-infected cells by the cellular immune system should be investigated before embarking in complicated mechanistic studies.

- **Conclusion**

— Summary

The committee feels this is a very good team.

— Strengths and opportunities

- Strong involvement in clinical research.

- Recognized national expertise of the PI in the field of indolent B cell lymphomas.

- Very good publication record in specialty journals.

- The excellent ability of the team leader to build scientific networks and to foster scientific interactions.

- The implication of the team leader in structuration of immuno/hematological research at the local and national level.

— Weaknesses and threats

- The lymphoma project remains highly descriptive.

- The overall project on EBV requires clarification.

— Recommendations

- Focus on hypothesis-driven projects.

- To increase its competitiveness, team 2 should define more rational strategies.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
PHYSIOLOGIE MOÉLCULAIRE DE LA RÉPONSE IMMUNE ET DES LYMPHOPROLIFÉRATIONS	**A**	**A+**	**A+**	**A+**	**A+**
GÉNÉTIQUE MOLÉCULAIRE DE LA CELLULE B ET DES SYNDROMES IMMUNOPROLIFÉRATIFS [COGNE-COGNE]	A+	A+	Non noté	A+	A+
MÉCANISMES MOLÉCULAIRES DE LA LYMPHOMAGÉNÈSE [COGNE-FEUILLARD]	A	A	Non noté	A	A

C1 Qualité scientifique et production
C2 Rayonnement et attractivité, intégration dans l'environnement
C3 Gouvernance et vie du laboratoire
C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

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Limoges, 6 avril 2011

To the president of the AERES evaluation committee
for the research unit "Physiologie moléculaire de la réponse immune et des lymphoprolifératıons"
University of Limoges / CNRS

Pr. Michel COGNE

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Dear colleague,

We acknowledge receipt of the AERES report for our unit. We first would like to thank the committee members for their thorough evaluation of our activity as well as for their encouraging comments and useful recommendations for both teams.

Answers to the general recommendations :
- We agree that we have to focus on a limited number of projects and our goal will thus be to go deeper into our current themes.
- We also consider as a priority to further develop partnerships
- We thank the committee for the recommendation of journal clubs; we set up such clubs twice a week since last february after this recommendation and the whole unit is very enthusiastic about it.

Answers to specific recommendations to Team 1:
We agree to focus on a limited number of projects in order to go as deep as possible in the physiological implications obtained from our transgenic models, including by further developing interactions with our external partners and increasing partnership with Team 2.

Answers to specific recommendations to Team 2:
- Regarding the MZ lymphoma project: Based on our results on human tumours, we start a mouse model project bridging Team 2 with Team 1 about the question of continuous NF-κB and/or BCR activation.
- Regarding EBV / B7-H1: Following the committee recommendation, we will finish the B7-HI experiments and refocus on the EBV control of apoptosis.
- Regarding the high competition in the EBV field: in addition of our previous publications, please note our recent EBV paper in ***Blood****, and note that our recent work on EBV/NFκB was selected for oral communication at the next Keystone Symposium on B-cells**.

*: **Jaccard A, Gachard N,** Marin B, Rogez S, Audrain M, Suarez F, Tilly H, Morschhauser F, Thieblemont C, Ysebaert L, Devidas A, **Petit B,** de Leval L, Gaulard P, **Feuillard J, Bordessoule D,** Hermine O; GELA and GOELAMS Intergroup. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study.
Blood. 2011 Feb 10;117(6):1834-9.

: **A Chanut, S Durand-Panteix, N Weinbreck, **I Youlyouz-Marfak, D Bordessoule, J Feuillard, and N Faumont.** Differential weight and function of RelA and RelB NF-kB complexes in both EBV-Transformed B-cells and Activated B-Cell-like Diffuse Large B-Cell Lymphomas: Keystone symposium on B Cells: New Insights into Normal versus Dysregulated Function, Apr 12 - Apr 17, 2011, Fairmont Chateau Whistler, Canada

With best regards,

Michel Cogné

Le Président de l'Université

Jacques FONTANILLE